1

SENSORY CONNEXIONS TO THE HYPOTHALAMUS AND MID-BRAIN, AND THEIR ROLE IN THE REFLEX ACTIVATION OF THE DEFENCE REACTION

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It has long been known that the behavioural and autonomic responses characteristic of flight or attack are integrated by structures in the hypothalamus and nearby mid-brain (Cannon & Britton, 1925; Bard, 1928). The responses appear in acutely decerebrated or decorticated cats without any deliberate stimulus being applied, and have been termed 'sham rage'. Bard (1928) mentioned the possibility that the responses might arise in such preparations from afferent impulses set up at wound edges and impinging on the brain-stem structures concerned; but both he and Cannon discussed their findings mainly in relation to Hughlings Jackson's (1898) concept that elimination of higher parts of the brain releases the activity of lower parts. They thus gave the impression that some spontaneous or tonic activity of the brain stem was being revealed in these experiments.

Hess, whose detailed work led to the location of precise brain-stem areas for integration of many basic behavioural patterns, also seemed to regard responses such as flight or attack—which he called the defence reaction—as automatic activities of the hypothalamus which could be inhibited or facilitated from higher parts of the brain (Hess & Brügger, 1943). Yet Woodworth & Sherrington (1904) had observed long before that several components of the whole reaction to nociceptive stimulation in the cat could be obtained as a stereotyped response to stimulation of the sciatic nerve shortly after pre-collicular decerebration. They characterized this as a reflex response and called it the pseudaffective reflex. Recently it has been shown that if section of the brain stem is made at a slightly higher level, so as to spare the hypothalamus, the reflex response then obtained, even in an acute preparation, comprises most of the features of the defence reaction (Abrahams, Hilton & Zbrozyna, 1960*b*). In the chronic decorticate preparation, as first exemplified by Goltz's (1892) dogs, such reactions persist as stereotyped responses to given stimuli, quite unchanged so long

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1

as the animal survives. Thus, there is every reason to consider these complex, autonomic and behavioural patterns of response as reflexes.

It is surprising, therefore, that, following the discovery of sensory pathways which impinge upon the brain stem (Starzl, Taylor & Magoun, 1951b), the role of such pathways has been considered mainly in relation to the concept of the reticular activating system; and their possible significance as the afferent pathways of specific brain-stem reflexes has never yet been seriously considered. This was the hypothesis, however, which led us to carry out experiments to see whether the brain-stem regions which constitute the integrative centre for the defence reaction have the sensory input necessary for them to function as a reflex centre, in the usually accepted sense of this term.

It was clear from previous work that potentials could be evoked in part of the mid-brain structures involved, in response to nociceptive stimulation (French, Verzeano & Magoun, 1953a) and flashes of light (Ingvar & Hunter, 1955), and in part of the hypothalamic structures in response to nociceptive stimulation (Dell, 1952; Feldman, van der Heide & Porter, 1959). But a large part of the centre for the defence reaction remained to be explored systematically for responses evoked by different sensory modalities.

In the present experiments, we have found that responses can be evoked in all parts of the integrative centre for the defence reaction to brief electrical pulses applied to the superficial radial nerve or to the skin itself, to single flashes of light to the eye and to single clicks. Thus, the afferent connexions do exist which would enable these brain-stem regions to function as a reflex centre for the defence reaction.

METHODS

Most of the experiments were performed on cats anaesthetized with chloralose in a single intravenous dose of 60 mg/kg, after preliminary induction with ethyl chloride and ether. In two cats pentobarbitone (30 mg/kg) was used instead. The electrodes used for recording were placed by conventional stereotactic methods. The exact electrode positions were determined after fixation of the brain in situ by examination of frozen sections of the brain, stained by the Luxol Fast Blue technique of Klüver & Barrera (1953).

Metal micro-electrodes were used, with tip diameters ranging from 1 to 10 μ. They were made from tungsten wire or stainless-steel surgical needles by electrolytic erosion (Hubel, 1957; Green, 1958). The conventional techniques of amplification and recording were used. Auditory stimuli consisted of clicks, generated by passing a square wave through a rochelle-salt crystal, or in later experiments, through a crystal microphone insert. Two sources of visual stimuli were used, either a miniature neon lamp, or a miniature incandescent lamp (L.E.S. 12 V, 0·75 W, Radiospares) driven directly from a stimulator. When the incandescent bulb was used, the flash produced was monitored by a phototransistor placed in close apposition to the bulb. The output from the phototransistor was displayed on one beam of the double-beam oscilloscope. In most experiments the light source was mounted close to one eye, the pupil of which had previously been dilated by the local instillation of a 1 %

solution of atropine sulphate. When small, restricted areas of the retina were to be stimulated, the light source was mounted on a perimeter, and by the use of apertures of varying diameter the angle subtended by the light source could be controlled. The eye being illuminated was secured to a ring by a few stitches in the sclera, and the other eye was occluded by a tin-foil cup.

For cutaneous stimulation single shocks were delivered either to the superficial radial nerve, or through a pair of needles inserted subcutaneously. In some experiments the action potential generated in the superficial radial nerve was monitored by a pair of electrodes placed proximal to the site of stimulation. When cutaneous stimulation led to small reflex muscular movements, either decamethonium iodide (100 μg/kg) or gallamine triethiodide (Flaxedil, 3 mg/kg) was injected and the animal maintained on artificial respiration.

In some experiments the cerebral cortex was removed under chloralose anaesthesia, either by undercutting with a scalpel or by means of a suction apparatus. In all these experiments, arterial blood pressure was continuously monitored by a Statham strain-gauge manometer connected to one femoral artery.

<div align="center">RESULTS</div>

<div align="center">*Distribution of evoked potentials*</div>

In a previous investigation it had been concluded that certain regions of the hypothalamus, central grey matter and mid-brain tegmentum function as a reflex centre for the defence reaction (Abrahams *et al.* 1960*b*). These regions have been explored in cats anaesthetized with chloralose. All regions were explored in eight cats, the hypothalamus alone in nine, and the mid-brain alone in three.

Electrical potentials were evoked in all these regions by cutaneous, auditory and visual stimuli. This has been demonstrated under other experimental conditions for the posterior hypothalamus, central grey matter and mid-brain tegmentum (Starzl *et al.* 1951*b*; Dell, 1952; Ingvar & Hunter, 1953; Feldman *et al.* 1959). We recorded, in addition, responses from more anterior regions of the hypothalamus, extending into the pre-optic region of the brain stem. Their distribution is illustrated in Fig. 1, in which they are plotted on diagrammatic sections of the pre-optic region (*A*) and at the chiasmatic (*B*) and tuberal (*C*) levels of the hypothalamus. The sections on the right show, for comparison, the region at each level from which the defence reaction is elicited on electrical stimulation. It can be seen that the centre for the defence reaction occupies only a small part of the region from which evoked responses can be obtained. This was found to be true also for the posterior hypothalamus, the central grey matter and mid-brain tegmentum.

Potentials were consistently elicited in all regions explored in response to cutaneous stimulation. In the experiments in which the superficial radial nerve was stimulated directly, the action potential was monitored and it was found that the responses resulted from conduction centrally by nerve fibres of the *A*δ group.

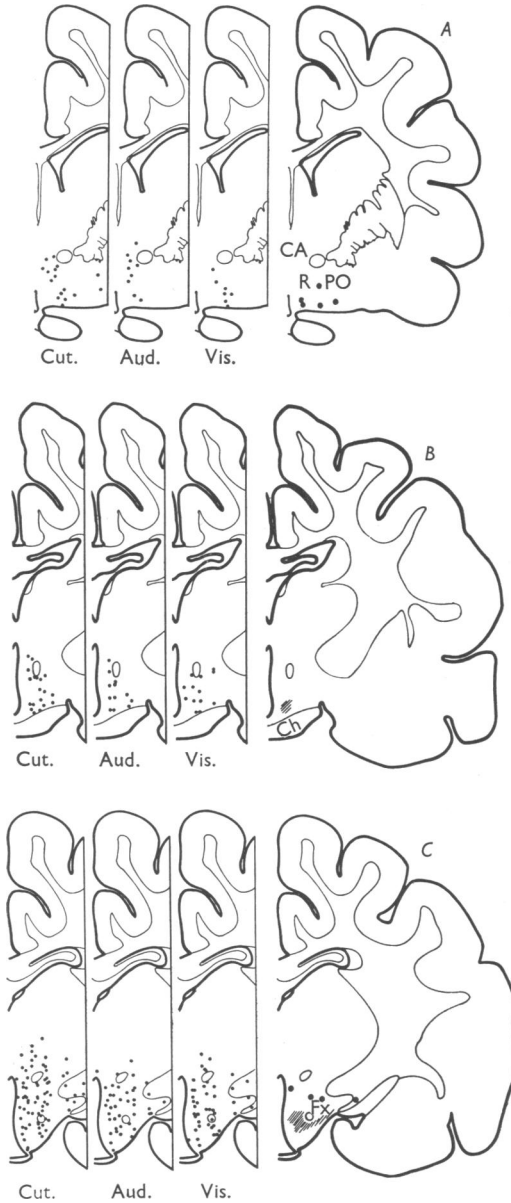Responses to auditory stimuli were only seen in 8 of the 20 experiments,

Fig. 1. Diagrammatic coronal sections at three levels of cat's hypothalamus to show points at which evoked potentials have been recorded. *A*, pre-optic region; *B*, level of optic chiasma; *C*, tuberal region of hypothalamus. Extreme right-hand section shows regions concerned with defence reaction (from Abrahams *et al.* 1960 *b*), hatched region being that from which responses are regularly obtained and dots indicating sites of responses obtained in individual experiments. The three panels to the left of each semisection show distribution of evoked potentials in response to cutaneous (Cut.), auditory (Aud.) and visual stimulation (Vis.). *CA*, anterior commissure; Ch, optic chiasma; Fx, fornix; RPO, pre-optic area.

but in these 8 experiments the responses were found in all the regions explored. This suggests that the absence of responses in the remaining experiments was due to damage of the middle ear by the ear bars used to fix the head.

Responses were evoked by visual stimuli in all but one experiment. In any single experiment responses were not always seen in all the regions explored, but as shown in Fig. 1, when the results from all 20 experiments were put together, the responses were distributed throughout the centre
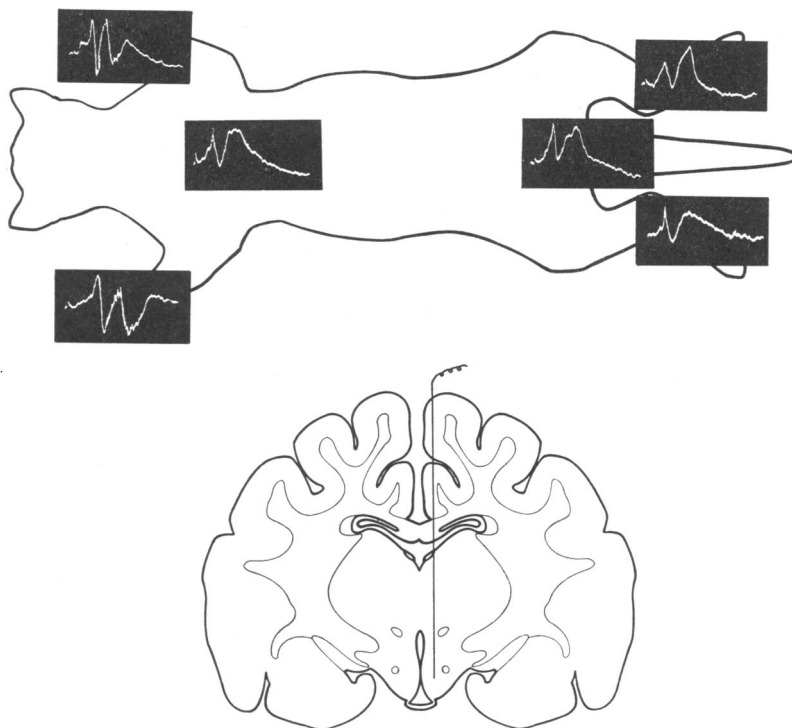

Fig. 2. Potentials evoked by electrical stimulation of different areas of skin. Above: diagram indicating site of cat's skin stimulated, with the potential evoked. Below: diagrammatic coronal section of cat's brain through tuberal region of hypothalamus showing position of recording electrode tip, medial to fornix.

for the defence reaction. The amplitude of these potentials depended on the area of retina illuminated. An increase of the illuminated area from 1 to $10°$ was sufficient to increase the amplitude of the evoked potential.

The electrical responses obtained by recording from any one point in the brain stem were little altered by changing the position of the source of stimulation. Figure 2 shows the responses recorded at a single point in the hypothalamus on electrical stimulation of six widely separated regions of

the skin, on each of the extremities, at the root of the tail and between the scapulae. Similarly, when small restricted regions (1°) of the retina of one eye were illuminated, as shown on the perimeter diagram in Fig. 3, similar evoked responses were seen at a single recording site whichever retinal region was illuminated.

This evidence of convergence within a single sensory system was complemented by evidence of convergence between systems. The experiments
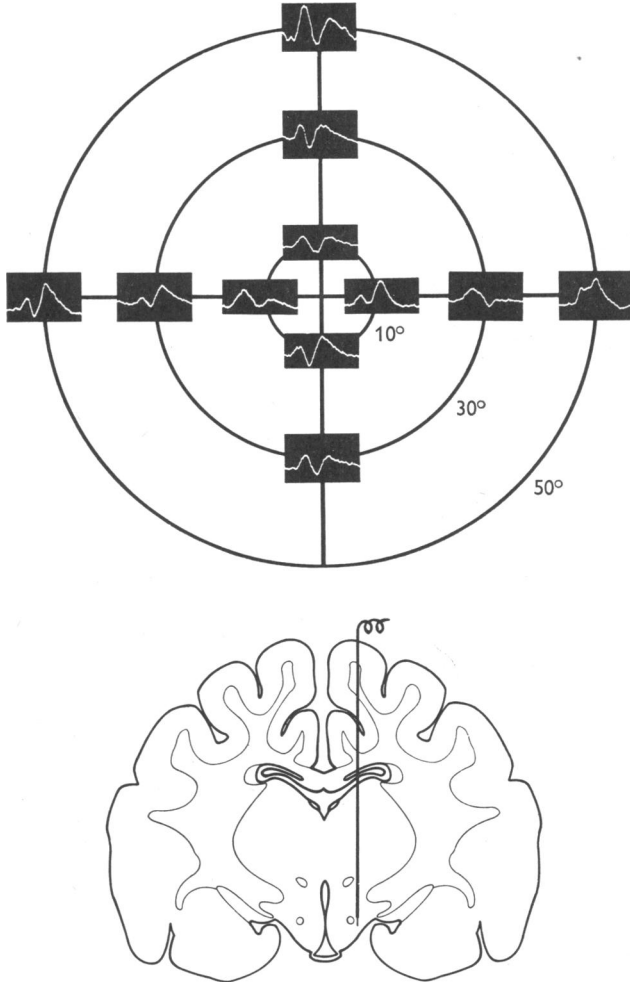

Fig. 3. Potentials evoked by flashes of light, illuminating 1° of retina. Above: perimeter diagram with evoked potentials superimposed on the position of the light source. Below: diagrammatic coronal section of cats' brain through tuberal region of hypothalamus showing position of recording electrode tip, lateral to fornix.

of Starzl *et al.* (1951*b*), Scheibel, Scheibel, Mollica & Moruzzi (1955) and Amassian & Waller (1959) had shown considerable convergence of the sensory pathways which relay into the mesencephalon and diencephalon, and this was readily demonstrated in the present experiments. In four cats the effect was examined of a response evoked by one sensory system upon the response evoked shortly after by a different system. Evidence of interaction between responses was obtained in tests carried out in the
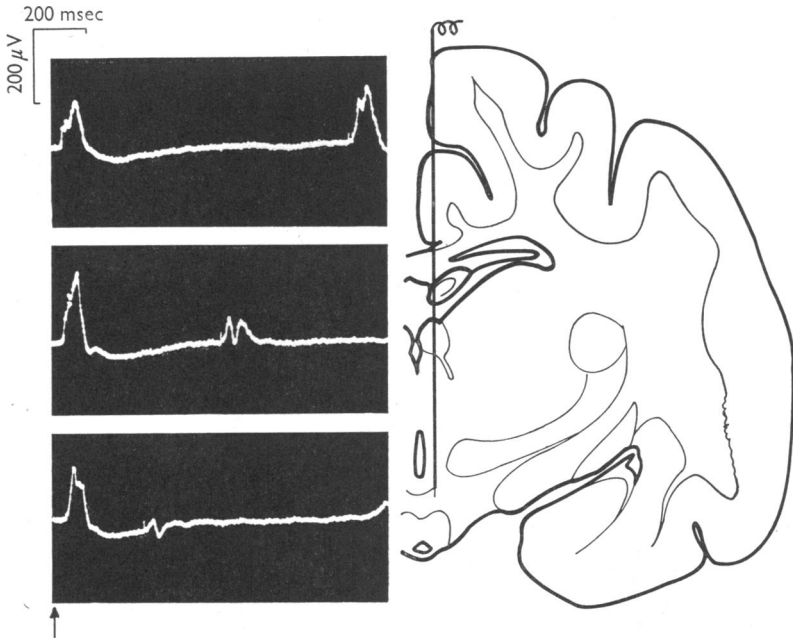

Fig. 4. Interaction of potentials evoked by different stimulus modalities. Potentials recorded dorsal to mammillary body (as shown in diagrammatic coronal section on right), in response to click (at arrow) followed by electrical stimulation of forepaw skin (stimulus shown by artifact).

hypothalamus, superior colliculus, central grey matter and adjacent tegmentum in that the second response was reduced or abolished when the interval between the stimuli was sufficiently short. In Fig. 4 this is shown for a response to cutaneous stimulation following one to a click. When skin stimulation follows the click with an interval of 340 msec between click and cutaneous stimulation, the response to the latter is just distinguishable above the background. In several interaction experiments, when the second response was reduced to this extent, a brief spike of short latency still remained, possibly due to impulses in fibres running near the tip of the electrode.

Characteristics of the evoked potentials

The evoked potentials were complex, of long duration and were considerably affected by the fluctuations of potential which occurred in the absence of deliberate stimulation. The potentials evoked by cutaneous and auditory stimulation were not consistent in form from one animal to another, neither were they related to the location of the electrode tip. Potentials evoked by visual stimulation were more consistent, frequently appearing as a double-peaked negative wave.
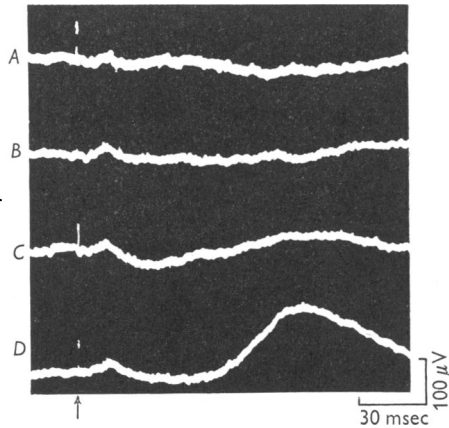

Fig. 5. Appearance of evoked potentials after administration of small doses of chloralose to a cat anaesthetized with pentobarbitone (30 mg/kg). Potentials recorded at single site in hypothalamus in response to shocks delivered to forepaw skin (at arrow). Records taken before (A) and after i.v. administration of chloralose, 3·5 mg/kg (B), 7 mg/kg (C), and 10·5 mg/kg (D).

Whereas potentials in lemniscal pathways in the brain stem are relatively resistant to anaesthetics, those in extralemniscal pathways are readily reduced or abolished by agents such as nitrous oxide, ether, pentobarbitone and cyclopropane (French, Verzeano & Magoun, 1953b; Randt, Collins, Davis & Dillon, 1958). In two cats anaesthetized with pentobarbitone (30 mg/kg) extensive explorations revealed only occasional, small evoked potentials. Further, in cats under chloralose anaesthesia the potentials were considerably reduced by intravenous injection of 3–4 mg/kg of pentobarbitone. In cats anaesthetized with pentobarbitone, chloralose was found to antagonize the depression of the activity of the extralemniscal system produced by the barbiturate. The successive sweeps of Fig. 5 show the gradual appearance of a response to cutaneous stimulation as small doses of chloralose (3·5 mg/kg) were given intravenously to a cat anaesthetized with pentobarbitone.

This is evidence of a facilitatory effect of chloralose on the neurones of the afferent pathway, but, in addition, these experiments show one of the sites where chloralose exerts a blocking action. Electrical stimulation via electrodes stereotactically placed in the same brain-stem regions readily elicits all the autonomic components of the defence reaction in cats under chloralose. Nevertheless, even following intense cutaneous stimulation in such cats it is not possible to obtain the autonomic components of the defence reaction reflexly (Abrahams *et al.* 1960*b*). It therefore appears that one of the sites of action of chloralose is at the synapses between afferent and efferent pathways in the brain-stem centre for the defence reaction.

Latencies of evoked potentials

In individual animals differences were recorded in the latencies of the responses, according to the site of the recording electrode and the sensory system being activated. The latencies also depended on the polarity of the initial component, being shorter when this was negative-going. In 19 experiments, in which latencies were measured of responses to electrical stimulation of the skin of the fore or hind limbs, the values lay between 6 and 16·5 msec. In most experiments the latencies tended to be shorter in the central grey matter than in the hypothalamus, and so in two cats a large number of observations were made of latencies in both brain-stem regions. Only responses with an initial negative-going component were compared. The mean value for the latency in the central grey matter was shorter than that in the hypothalamus by 3·9 msec ($t = 8·696, P < 0·001$) in one experiment and 6·1 msec ($t = 11·05, P < 0·001$) in the other. The latencies of the responses evoked in the hypothalamus were, of course, longer than those recorded in the somatic sensory cortex. In 2 experiments potentials were recorded simultaneously at a point in the hypothalamus and at a site on the precruciate region of the cerebral cortex where the shortest latencies were found. The latency of the cortical responses was always less than that of the corresponding hypothalamic response, the mean difference being 4 msec in one experiment and 5·1 msec in the other.

The latencies of the responses to auditory stimulation ranged from 10 to 22 msec, there being no consistent difference in the values recorded in the various brain-stem regions. The responses to visual stimulation appeared with longer latencies—from 40 to 50 msec in all regions—except for the hypothalamus where they were as short as 30 msec in one experiment and as long as 68 msec in another.

Evoked potentials after removal of the cerebral cortex and basal ganglia

In four cats under chloralose anaesthesia decerebration was performed at a high level with the intention of removing most of the brain lying

dorsal and anterior to the hypothalamus. The recording electrode was then inserted into the various regions of the brain stem. In all experiments cutaneous stimulation evoked responses in the relevant mid-brain regions: that is, in the central grey matter and the adjacent tegmentum. This is illustrated by the results shown in Fig. 6. Auditory stimulation evoked responses in these regions in only one cat, but in no experiment were responses obtained to visual stimulation. In 3 of the experiments the line of section encroached upon the hypothalamus, and evoked potentials were
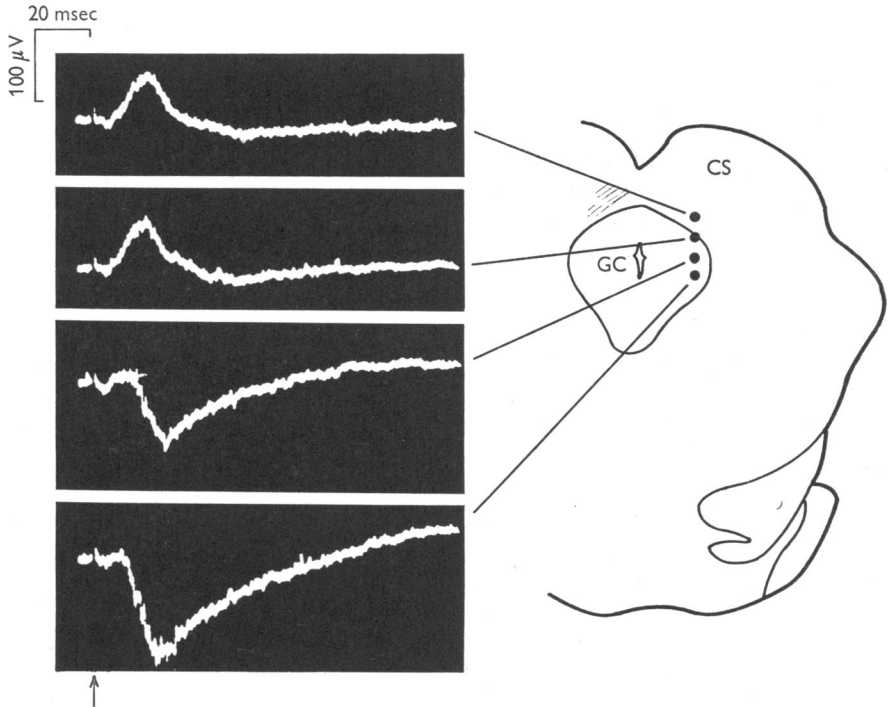

Fig. 6. Responses evoked by cutaneous stimulation (at arrow), recorded at four points in the mid-brain of a cat decerebrated under chloralose anaesthesia. GC, central grey matter; CS, superior colliculus.

not recorded in this region. In the remaining cat the hypothalamus was intact and potentials were evoked in this part of the brain stem by cutaneous stimulation, but not by auditory or visual stimuli. The responses to cutaneous stimulation were recorded from sites both in the tuberal and pre-optic regions, an example from the tuberal region being shown in Fig. 7.

In five cats under chloralose anaesthesia the cerebral cortex was removed in stages by suction. A recording electrode had previously been introduced into the hypothalamic region and evoked potentials obtained. This

electrode was left *in situ* during removal of the cortex. The advantage of this method is that it allows the potential to be followed through successive stages of the decortication, although it is difficult to avoid damage to the brain stem by movements against the electrode, particularly when the cortex in the vicinity of the electrode is being removed. Nevertheless, in every experiment the cutaneous evoked responses survived removal of the pericruciate area and the orbitofrontal cortex anterior to it, regions which include the primary and secondary cortical receiving areas. Similarly,
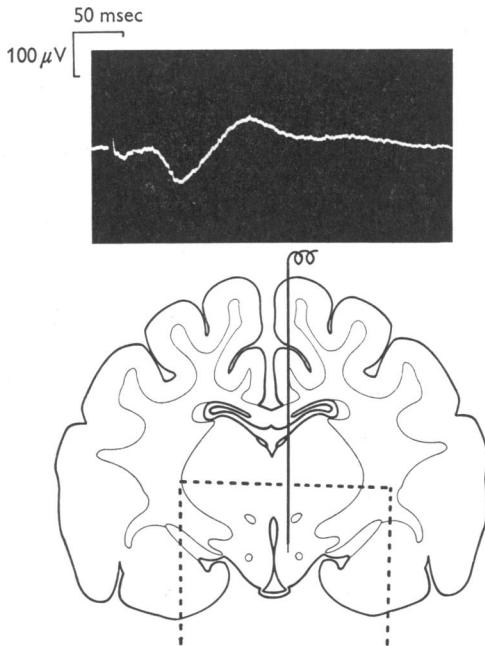

Fig. 7. Above: potential evoked by cutaneous stimulation in hypothalamus of cat decerebrated under chloralose anaesthesia. Below: diagrammatic coronal section through tuberal region of hypothalamus showing position of recording electrode, medial to fornix. The brain dorsal and lateral to the dotted line had been removed before insertion of the recording electrode.

visual responses survived removal of the striate region and a large area of surrounding cortex, including the whole of the occipital lobe. In 2 out of the 5 experiments the response to cutaneous stimulation survived the removal of nearly the whole of the cerebral cortex. In one of these the visual response also survived (Fig. 8): in this experiment only the superficial layers of the cerebral cortex had been removed.
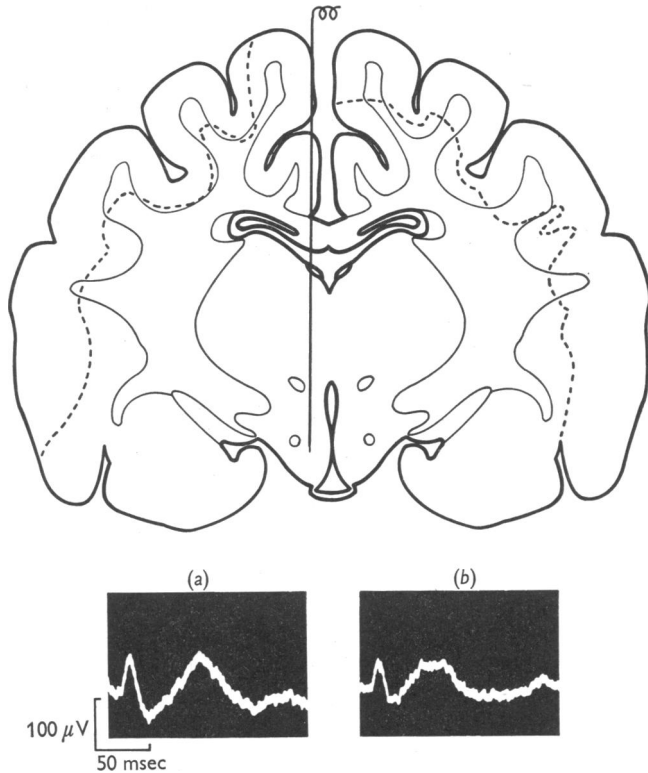
Fig. 8. Potentials evoked by flash of light before and after almost complete removal of superficial layers of cerebral cortex of cat under chloralose anaesthesia. Above: diagrammatic coronal section through tuberal region of hypothalamus showing position of recording electrode, medial to fornix, and extent of removal of cerebral cortex (shown by dotted line) at this level. Below: potentials evoked (a) before and (b) after decortication.

DISCUSSION

This investigation has been primarily concerned with the afferent pathways by which the defence reaction can be elicited reflexly. The term 'defence reaction' is here used to include not only the fully developed responses of flight or attack, but also the alerting response; for the evidence suggests that the regions in the hypothalamus, central grey matter and mid-brain tegmentum concerned in the integration of all these responses are the same; the responses simply represent different stages in a graded reaction. Hess & Brügger (1943) showed that the response to threshold electrical stimulation of these regions of the brain is alerting, and that if the stimulus is prolonged or its intensity increased the reaction progresses to flight or attack. When the visceral signs of the defence reaction are taken into account, most of them are seen to be fully developed during the

early stages of the response, when the only outward sign is alerting, no matter whether the alerting is produced by direct electrical stimulation of the brain stem or by a stimulus from the external environment such as a loud noise. This applies not only to such features of the response as pupillary dilatation and the rise in arterial blood pressure, which are not specific to the defence reaction; but also to the atropine-sensitive muscle vasodilatation that Abrahams, Hilton & Zbrozyna (1960*a*, *b*) have shown to be a characteristic and invariable component, which is well developed during alerting.

The appearance of evoked potentials in all these regions in response to cutaneous, auditory and visual stimuli provides direct evidence of relays from all three systems converging on the appropriate brain-stem regions. It might be questioned whether the widespread distribution of the evoked potentials arose in part from an action of chloralose. However, when explorations have been made in similar regions of the cat's brain without the use of any anaesthetic, the same distribution of evoked potentials has been observed (e.g. Starzl *et al.* 1951*b*; Feldman *et al.* 1959). Our results, therefore, may be taken to indicate that the afferent connexions exist which would enable the brain-stem regions concerned to act not simply as an integrative centre but, indeed, as a reflex centre for the defence reaction.

The characteristic features of the evoked potentials were their long latencies, sensitivity to barbiturate anaesthesia and persistence after acute removal of the cerebral cortex. Potentials with these features have been reported previously in the mid-brain of the cat and monkey (Starzl *et al.* 1951*b*; French *et al.* 1953*a*, *b*). Starzl *et al.* (1951*b*), who coined the term 'afferent collateral system' for the multineurone pathway giving rise to evoked potentials of this kind, believed this to be an afferent system which activates large regions of the brain stem, so that these in turn can maintain the cerebral cortex in a state of 'alertness'. Thus the function of these parts of the brain stem has come to be considered mainly in relation to the concept of the ascending reticular activating system (Lindsley, Bowden & Magoun, 1949; Starzl, Taylor & Magoun, 1951*a*). It was recognized that these parts of the brain stem can influence motor, autonomic and endocrine activity (Magoun, 1958), but attention has been concentrated on one single manifestation of their activity. Yet there is evidence from several sources, established over many years, which points to the role of these regions as centres of complex, co-ordinated reflex responses, integrating the autonomic and behavioural patterns of alimentary and sexual reflexes, as well as of the defence reaction (Goltz, 1892; Woodworth & Sherrington, 1904; Bard & Rioch, 1937; Bard, 1940). The reflex centre for the defence reaction itself occupies a major part of the

brain-stem regions hitherto considered mainly in relation to the reticular activating system (Abrahams *et al.* 1960*b*) and the behavioural alerting which results from activation of these regions is readily explained as a manifestation of the defence reaction. The afferent limb of the uncondi- tioned reflex is thus seen to lie in the pathway which has been termed the afferent collateral system.

In cats with extensive mid-brain lesions responses to noxious stimuli are grossly impaired (Hunsperger, 1956; Sprague, Chambers & Stellar, 1961). Sprague *et al.* (1961), who kept their cats for long periods of time after the lesions had been made, found that their animals did not respond to electric shocks, to inhalation of high concentrations of ammonia or even to attack by dogs. They attributed this result to interruption of the classical sensory (lemniscal) pathways. It is clear from the diagrams they present, however, that their lesions occupied most of the mid-brain structures which we have identified as the reflex centre for the defence reaction, which would have resulted in the destruction of a large part of the reflex centre and of the sensory inflow leading to it.

Conversely, when the part of the brain above the brain-stem centre for the defence reaction regions has been removed, all, or at least many, of the features of the defence reaction are regularly obtained as stereotyped reflex responses. These are seen on mild cutaneous stimulation of the chronic decorticate or decerebrate cat or dog (Goltz, 1892; Dusser de Barenne, 1920; Keller, 1932; Bard & Rioch, 1937), and in response to a loud noise, even in the chronic mid-brain cat (Bard & Macht, 1958). Consonant with these earlier observations, the potentials evoked by activation of these sensory systems were found to converge on the appro- priate parts of the brain stem and to survive decortication or high decere- bration. They were obtained in the hypothalamus in response to cutaneous stimulation when all the brain above had been removed, showing that the cutaneous afferent pathways were intact and functioning. When the line of section encroached on the hypothalamus, evoked potentials were no longer obtained. This failure of conduction in the afferent pathway could explain why Abrahams *et al.* (1960*b*) were able to obtain active muscle vasodilata- tion in only a proportion of their acute decerebrate cats, when eliciting the pseudaffective reflex response to peripheral nerve stimulation.

The defence reactions of chronic decorticate cats and dogs are a striking feature of their response to gentle handling (Goltz 1892; Dusser de Barenne, 1920). From Goltz's description of his decorticate dogs, for instance, their response to such a trivial stimulus as stroking the skin is clearly identical with the fully developed defence reaction. This response was elicited with undiminished vigour, day after day, as long as the animals lived. Thus, in the decorticate animals in which the reflex mechanism underlying the

defence reaction, including the collateral afferent pathway, is intact, but the projections of the classical sensory pathways are removed, defence reflexes are continually produced, as stereotyped responses, even to hardly noxious stimuli. A characteristic feature of the decorticate preparation, therefore, is the absence of inhibition as normally manifested in the phenomenon of habituation. In the normal cat the alerting produced by any sudden stimulus, such as the sound of a buzzer, soon disappears with repetition of the stimulus. This is true also for the defence reactions in response to weak noxious stimuli. Here we can see a possible significance of the slowness of conduction in the collateral afferent system, reflected in the long latencies of the evoked responses, as compared with the much shorter latencies of the cortical evoked responses. The inhibitory pathway which underlies the phenomenon of habituation involves the cerebral cortex. Nevertheless, impulses set up in this inhibitory pathway must arrive at the reflex centre, and so depress its excitability, *before* impulses travelling in the multineurone pathway impinge on the centre. It is possible that transmission is inhibited in the multi-neurone pathway itself.

SUMMARY

1. In cats anaesthetized with chloralose, cutaneous, auditory and visual stimuli evoke potentials in widespread regions of the hypothalamus, central grey matter and mid-brain tegmentum.

2. These potentials appear after relatively long latencies. They are reduced or abolished by small amounts of pentobarbitone, but survive removal of the cerebral cortex.

3. Convergence of the afferent pathways is indicated by considerable interactions obtained between potentials evoked by different sensory systems. There is also convergence within the afferent pathways of a single system.

4. The multineurone pathway giving rise to these potentials is apparently identical with that originally termed the afferent collateral system, which is usually considered in relation to the concept of the ascending reticular activating system. It is suggested, however, that the significance of this pathway lies chiefly in connexion with complex reflexes organized at the level of the hypothalamus and mid-brain, such as the defence reaction, and that it constitutes the afferent limb of the unconditioned reflex.

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